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AFRRI SCIENTIFIC REPORT

Effects of ^{60}Co radiation on synthesis of prostaglandins $F_{2\alpha}$, E, and thromboxane B_2 in lung airways of guinea pigs

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20. ABSTRACT (continued)

divalent cation transport stimulation with ionophore. Tissues from irradiated animals demonstrated alterations in the amount and type of prostaglandins generated, varying with time postirradiation.

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Effects of ^{60}Co Radiation on Synthesis of Prostaglandins $F_{2\alpha}$, E, and Thromboxane B_2 in Lung Airways of Guinea Pigs[1,2]

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INTRODUCTION

Recent evidence suggests that ionizing radiation induces dramatic changes in prostaglandin (PG) levels in animal tissues (*1–5*) and body fluids[4] (*6, 7, 42*). The pharmacological properties of the prostaglandins, coupled with enhanced formation and release in all types of inflammatory reactions (*8–10*), suggest a role for these chemical mediators in the development of radiation-induced tissue injury. The lung is a major site of prostaglandin production (*11, 12*), uptake (*13, 14*), and inactivation (*14–16*). Following exposure to ionizing radiation, numerous biochemical and histopathological changes are manifested in pulmonary structures and fluids [for reviews, see (*17–19*)]. In a recent communication (*5, 20*) we examined the effects of γ radiation on prostaglandin and thromboxane levels in parenchymal lung tissues and found the magnitude of alteration to increase in a dose-dependent manner. Altered responsiveness to H-1 receptor stimulation with histamine and to the ionophore stimulation of divalent cation transport also occurred in parenchymal tissues. Since the PGs have

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[2] Research was conducted according to the principles enunciated in the *Guide for the Care and Use of Laboratory Animals*, prepared by the Institute of Laboratory Animal Resources, National Research Council.

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been implicated in the modulation of pulmonary vascular and airway function (*8, 21, 22*), we directed our efforts toward elucidating the contribution of the lung bronchial tree in the bronchopulmonary functional response to radiation insult. The present investigation was performed to determine the effects of ^{60}Co γ radiation on levels of lung bronchial airway prostaglandin and thromboxane. Tissue capacity to synthesize PG in response to the exogenous addition of histamine or the calcium ionophore A23187 was also studied.

MATERIALS AND METHODS

Chemicals and Buffers

Tritiated prostaglandin $F_{2\alpha}$ ([^{3}H]$PGF_{2\alpha}$) (120 Ci/mmole), tritiated prostaglandin E_2 ([^{3}H]PGE_2) (150 Ci/mmole), and tritiated thromboxane B_2 ([^{3}H]TxB_2) (120 Ci/mmole) were obtained from New England Nuclear (Boston, MA). Rabbit $PGF_{2\alpha}$ antiserum and rabbit PGE antiserum were purchased from Clinical Assays (Boston, MA) and Accurate Chemical and Scientific Company (Somerville, NJ), respectively. Histamine diphosphate, Trizma (pH 7.4), and gelatin Bloom-100 were obtained from Sigma Chemical Company (St. Louis, MO); Norit-A from Fisher Scientific Company (Pittsburgh, PA); Ultrafluor scintillation cocktail from National Diagnostics (Somerville, NJ); and Dextran T-70 and protein A–Sepharose CL-4B from Pharmacia (Uppsala, Sweden). Ionophore A23187 was obtained from Calbiochem-Behring Corporation (La Jolla, CA). A23187 was dissolved in dimethylsulfoxide at a concentration of 10 mg/ml and diluted in buffer before use.

TxB_2 antiserum was prepared in rabbits. An IgG-rich fraction was produced by ammonium sulfate precipitation followed by affinity chromatography on a protein A–Sepharose CL-4B column.

Tyrode's buffer (137.0 m*M* NaCl, 2.7 m*M* KCl, 0.36 m*M* NaH_2PO_4, 5.55 m*M* dextrose, 11.9 m*M* $NaHCO_3$, 1.8 m*M* $CaCl_2$, and 0.49 m*M* $MgCl_2$, pH 7.8) was prepared just before use.

Irradiation of Animals

A total of 120 male guinea pigs (Hartley strain), weighing 550–650 g, were used throughout the investigation and maintained on Purina guinea pig diet and water *ad libitum*. Animals were arbitrarily divided into two groups of 60 animals each (sham and irradiated). For each irradiation, nonanesthetized guinea pigs were individually placed in a 25 × 10 × 10-cm Plexiglas restraining chamber. Four chambers were vertically stacked, allowing simultaneous exposure of four animals. The irradiated group was unilaterally exposed to 3.0 Gy of ^{60}Co radiation (1.17- and 1.33-MeV γ) at a dose rate of 39.5–40.7 rad/min (target distance 120 cm, tissue/air ratio, 0.91) using a Theratron-80.

Control guinea pigs were placed in restraining chambers and held in the exposure room for the same period of time as their irradiated counterparts. Treatment of controls differed only in that they did not receive the ^{60}Co exposure.

Preparation of Fragments from Guinea Pig Lung Airways

Exposed and sham-irradiated (control) guinea pigs were individually sacrificed at 1, 3, 6, 24, 48, 79, 96, 120, 168, or 336 hr postirradiation. Each was exsanguinated

and the thorax opened to expose the heart and lungs. Tyrode's buffer was instilled through the right atrium, and the lungs were infused until visually cleared of blood and clear fluid drained from the excised aorta. The lungs were quickly removed from the thorax and placed in buffer. Airway fragment preparations (6–8 mg wet weight) were prepared by removing all surrounding parenchymal tissue through meticulous dissection with fine forceps (Fig. 1). Histologic examinations of these airway preparations revealed very little contamination by adherent alveolar tissue. Nine airway fragments were obtained from each preparation of experimental animal airway. The lung airway fragments were placed in 50 ml prewarmed buffer and maintained undisturbed at 37°C for 45 min.

Generation and Determination of Prostaglandin (PG)

Airway replicates, equilibrated to 37°C in buffer, were individually transferred into separate 1.5-ml Eppendorf microfuge tubes containing 200 μl of prewarmed (37°C) test substance. Care was taken to ensure that each fragment was manipulated as gently as possible. Airways were exposed to histamine (5×10^{-4} *M*) (*27*), A23187 (*23*), or Tyrode's buffer alone [as a measure of spontaneous (basal) PG release], in triplicate experiments. The tissues were incubated for 30 min at 37°C in the test solutions. Incubation was terminated by removing the airway fragments from the supernatant medium and placing each in individual 1.5-ml Eppendorf tubes containing 1 ml of 0.1 *N* NaOH. Fragments were digested overnight at 40°C, and protein concentrations of the tissue digests were determined with the Folin reagent (*24*). The supernatants from incubated lung airway-challenge experiments were either immediately assayed for PG content or stored at −20°C and assayed for PG control within 5 days. Prostaglandin levels were determined by a modified procedure (*27*) of the radioimmunoassay technique of Jaffe *et al.* (*25*).

Briefly, the radioimmunoassay consists of incubating 20 μl (10% of the 200-μl incubation volume) of either supernatants of the challenged lung airway fragment or known standards (2.5–1000 pg) and 80 μl Trizma buffer (0.012% Trizma, 0.083% NaCl, 0.1% gelatin, pH 7.4) with 50 μl antisera for 2 hr at room temperature. Thereafter, 50 μl [^{3}H]PG (8000 cpm) was added and incubation continued at 4°C overnight (12–16 hr, final volume 200 μl). Following the addition of 250 μl Trizma–NaCl–gelatin (1.0%), the bound [^{3}H]PG was separated from the uncomplexed tracer by adding 500 μl iced charcoal (0.5%)–Dextran (0.05%) in Trizma–NaCl, incubating 20 min at 4°C, and centrifuging at 200*g* for 17 min at 4°C. The resulting supernatants were decanted into scintillation vials containing 10 ml Ultrafluor, and radioactivity was determined by scintillation counting (Mark III). All radioimmunoassays were performed in duplicate.

Presentation of Data and Statistics

Data are expressed as percentage release of control values. Results are given as the means ± SEM. Differences between challenges and corresponding control values for the same time interval were considered significant if, when combining the data from several experiments (blocking), comparison of two independent samples gave a probability (*P*) of less than 0.05 (*26*).

FIG. 1. Airway preparation of guinea pig lung. Airways were dissected free of adherent parenchyma and subsequently fragmented into airway replicates.

RESULTS

The effect of a single unilateral exposure to 3.0 Gy ^{60}Co γ radiation on basal prostaglandin $F_{2\alpha}$, E, and thromboxane B_2 levels in preparations of guinea pig lung airway was examined. As shown in Figs. 2A–C, tissues from sham-irradiated animals released PG into the incubating medium in a uniform fashion at each time point in the course of these investigations. Sham release values (pg/mg airway lung protein) ranged from 423 to 567 pg $PGF_{2\alpha}$, 130 to 158 pg PGE, and 1709 to 2152 pg TxB_2. Individual values at each time point did not statistically differ from other time point values for each respective PG throughout these studies. Airway tissues from animals that had received a single unilateral exposure to 3.0 Gy ^{60}Co γ radiation revealed no significant alteration in the quantity of TxB_2 released into the buffer medium at all time points studied, compared to sham-irradiated release (Fig. 2C). Likewise, irradiated tissue elaborated $PGF_{2\alpha}$ in response to buffer challenge in a manner not dissimilar to their sham-irradiated counterparts (Fig. 2A). A transient rise in $PGF_{2\alpha}$ basal release from irradiated tissues occurred at 48 hr postirradiation ($P = 0.043$) but it declined to control values at 72 hr. A dramatic elevation in PGE levels was noted in buffer-incubated irradiated tissues at 3 hr postirradiation; the levels returned to control levels by 6 hr. A rise in PGE levels was also observed at 24 hr in animals receiving 300 rad, but it was not statistically significant ($P = 0.052$). PGE levels in irradiated tissues did not differ from those observed in control tissues at 48 to 336 hr.

We examined the capacity of guinea pig airway lung tissue from irradiated and control animals to respond to H-1 receptor stimulation with 500 μM histamine (Figs. 3A–C). Sham-irradiated tissues consistently responded to histamine with significantly higher PG levels than matching airway replicates incubated in buffer only. Sham response to provocation with histamine, expressed as percentage of sham basal release (Fig. 2), ranged from 128 to 137% $PGF_{2\alpha}$, 148 to 167% PGE, and 116 to 127% TxB_2.

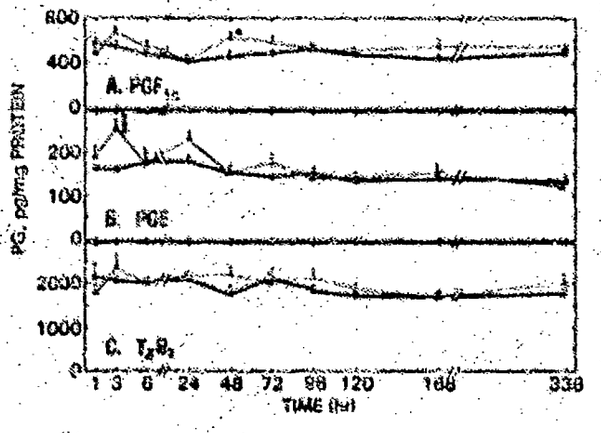

FIG. 2. Effect of 3.0 Gy ^{60}Co γ radiation on levels of basal $PGF_{2\alpha}$, PGE, and TxB_2 in tissues of guinea pig airway lung. Airway replicates were incubated in Tyrode's buffer only, as described in the text. Prostaglandin (PG) levels are given as picograms per milligram guinea pig airway protein. (A) $PGF_{2\alpha}$ levels; (B) PGE levels; (C) TxB_2 levels. Sham-irradiated (control) release, ●; irradiated, ▲. Means ± SEM are given; SE is indicated by vertical lines. $^{*}P < 0.05$; $^{***}P < 0.001$ (toward corresponding control). $n = 18$.

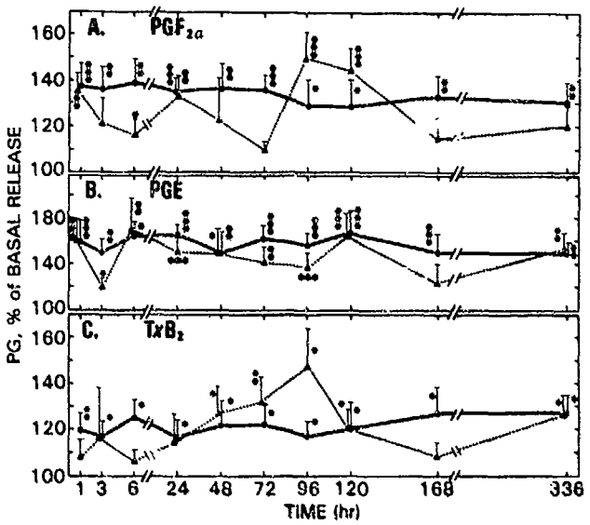

FIG. 3. Effect of 3.0 Gy ^{60}Co γ radiation on histamine-induced $PGF_{2\alpha}$, PGE, and TxB_2 levels in airway tissues. Airway replicates were incubated in Tyrode's buffer containing 5×10^{-4} *M* histamine, as described in the text. PG generation evoked by histamine challenge is expressed as percentage of each group's own basal PG release in Tyrode's buffer only (see Fig. 1). (A) $PGF_{2\alpha}$; (B) PGE; (C) TxB_2. Sham-irradiated (control) release, ●; irradiated, ▲. Means ± SEM are given; SE is indicated by vertical lines. Significant PG generation induced by histamine challenge (compared to buffer controls): $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. $n = 18$.

Tissues from animals receiving 3.0 Gy responded to histamine stimulation with variable PG release. At 3, 48, 168, and 336 hr postirradiation, tissues were not capable of generating significant $PGF_{2\alpha}$ synthesis in response to histamine challenge, compared to their own buffer control release (Fig. 3A). In this regard, the large variability in airway fragment responsiveness should be noted as a factor contributing to overall nonsignificant $PGF_{2\alpha}$ elevations at these time points. PGE levels evoked by histamine provocation were significantly elevated above buffer controls at all time points except 168 hr postirradiation (Fig. 3B). Airway tissues from irradiated animals were unresponsive to histamine challenge in terms of synthesis of TxB_2 at 1–24 hr postirradiation (Fig. 3C). Significant TxB_2 levels were generated at 48–120 hr, whereas at 168 hr, histamine was an ineffective stimulator of TxB_2 synthesis. At 336 hr, tissues again responded to histamine provocation with significant TxB_2 release above buffer-incubated matching airway replicates.

To determine the effects of ionizing radiation on the production of PG stimulated by the transmembrane transport of divalent cations, airway tissue preparations were challenged with the calcium ionophore A23187. The ionophore-stimulated release by $PGF_{2\alpha}$ and PGE from preparations of sham-irradiated airway was significantly higher than that of matching buffer-incubated fragments throughout these studies (Figs. 4A and B). PG levels, expressed as percentage of basal release (Fig. 2), ranged from 128 to 150% and 142 to 176% that of buffer-incubated tissue $PGF_{2\alpha}$ release and PGE release, respectively. The capacity of airway tissue from the irradiated group to respond to provocation by A23187 with $PGF_{2\alpha}$ or PGE release was curtailed at 3 and 6 hr postirradiation, but achieved significant synthesis at 24 hr. At 48 hr, PGE levels

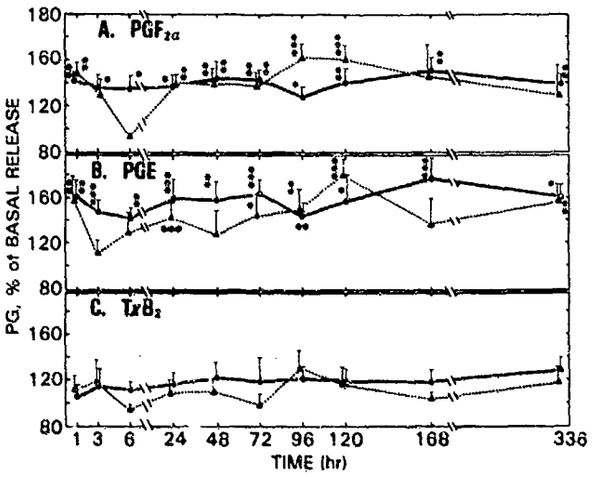

FIG. 4. Effect of 3.0 Gy ^{60}Co γ radiation on A23187-induced $PGF_{2\alpha}$, PGE, and TxB_2 levels in airway tissues. Airway replicates were incubated in Tyrode's buffer containing A23187 (25 μg/ml), as described in the text. PG generation induced by ionophore stimulation is expressed as percentage of each group's own basal PG release in Tyrode's buffer only (see Fig. 1). (A) $PGF_{2\alpha}$; (B) PGE; (C) TxB_2. Sham-irradiated (control) release, ●: irradiated, ▲. Means ± SEM are given; SE is indicated by vertical lines. Significant PG generation evoked by A23187 challenge (compared to buffer controls): $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. $n = 18$.

were not elevated above those of buffer-treated samples, but the airway tissues were capable of significant production of A23187-stimulated PGE at 72 hr. Ionophore challenge at 168 hr postirradiation did not evoke significant generation of PG; in contrast, at 336 hr, tissues were capable of significant synthesis of PGE (but not $PGF_{2\alpha}$).

Analysis of TxB_2 release by airway tissues from either sham-irradiated animals or those receiving 300 rad (Fig. 4C) revealed these tissues to be unresponsive to challenge with A23187. Tissues from control or irradiated groups were not capable of generating significant TxB_2 in response to ionophore challenge, compared to their respective buffer-incubated airway replicates (Fig. 2C).

DISCUSSION

Our results suggest that ionizing radiation induces a transient yet significant alteration in the generation of the prostaglandins $F_{2\alpha}$ and E by preparations of guinea pig bronchial airway. At 3 hr postexposure, significant elevation of basal PGE levels was observed, whereas a transient elevation of basal $PGF_{2\alpha}$ generation was seen at 48 hr postirradiation. The airway preparations used in these experiments, although essentially devoid of contaminating parenchymal tissues, consisted of a mixture of cell types. As a result, the prostaglandin levels reported herein reflect their overall synthesis, since the precise cellular source of the increased prostaglandins could not be established.

The transient elevation in levels of airway basal PGE at 3 hr postirradiation agrees with previously reported findings in other tissues and fluids. Liver and spleen from the rat (*4*) and mouse (*3*) demonstrate transiently elevated PGE synthesis at 3 hr

following ^{60}Co exposure. Exudates from normal skin of the human abdomen exposed to ultraviolet radiation contain elevated PG levels at 2–24 hr postexposure (*7*). Elevations in urinary levels of PGE (*42*) and TxB_2 (*6, 42*) in rats previously exposed to ^{60}Co have also been reported to occur at 3–4 hr postirradiation.

Prostaglandins are not stored but are synthesized by cells *de novo* prior to their release. Therefore, one might explain the rise in PGE levels as a vasodilatory response to the radiation-induced disruption of cellular membrane integrity and release of biologically active substances. Whereas PGE acts as a bronchodilator (*10*), $PGF_{2\alpha}$ exerts a vasoconstrictive action (*27*). Elevated PGE synthesis may reflect a defense mechanism of airway smooth muscle to counteract the contractile actions of biogenic amines (e.g., histamine) and other stimuli (*28, 29*). Subsequently, $PGF_{2\alpha}$ formation might favor smooth muscle contraction to counteract PGE-mediated bronchodilation. Interestingly, levels of $PGF_{2\alpha}$, PGE, and TxB_2 in guinea pig parenchymal lung tissue were all significantly elevated at 1–3 hr after exposure to 300 rad of ^{60}Co radiation (*5*). On the basis of our findings, one can only speculate on the relative contribution of the pulmonary vascular tissue in modulating or influencing airway response (or vice versa).

Guinea pig parenchyma preparations (*30, 31*) and airway preparations (*31*) have been demonstrated to synthesize PG in response to stimulation of H-1 receptor sites with histamine. In the studies reported in this communication, the capacity of bronchial airway tissues from irradiated animals to respond to histamine provocation with PG synthesis revealed alterations in the type and amount of prostaglandin generated. Tissue receptor responsiveness appeared to vary over time, but all three PGs exhibited differing patterns of generation in response to histamine stimulation. One notable exception was at 168 hr (7 days) postirradiation, when preparations of histamine-challenged bronchial airway did not synthesize significant quantities of $PGF_{2\alpha}$, PGE, or TxB_2 above their own buffer-treated controls.

The carboxylic acid ionophore A23187 has previously been demonstrated to evoke prostaglandin biosynthesis in a variety of cell types (*32*), including guinea pig parenchymal and airway lung tissues (*33*). This action is thought to result from A23187-promoted Ca^{2+} transport and the ensuing activation of Ca^{2+}-dependent phospholipases, which in turn enzymatically cleave arachidonic acid (parent compound of $F_{2\alpha}$, E, and TxB_2) esterified in membrane phospholipids. As our results show, bronchial airways from ^{60}Co-exposed animals respond to ionophore challenge in a manner somewhat similar to the pattern of $PGF_{2\alpha}$ and PGE release seen with histamine provocation. Just as control (sham-irradiated) airway tissues failed to generate significant TxB_2 synthesis in response to A23187 challenge, the irradiated tissues also did not respond. Thus it appears that bronchial airways do not generate TxB_2 in response to A23187 stimulation of unsaturated fatty acid metabolism.

The relationship of prostaglandin and thromboxane concentrations to radiation damage is unresolved. The lung is a primary organ for circulating prostaglandin uptake and degradation (*34, 35*) as well as a primary site of prostaglandin production in inflammatory reactions (*8–10*). Numerous tissue reactions resulting from radiation injury [including alterations in membrane surface tension properties, impairment of gas exchange (*36*), leakage of plasma protein (*37–39*), alterations in enzyme(s) activities responsible for PG synthesis or degradation (*40*), and greater radiosensitivity of certain lung cell types (*41*)] may in part account for the observed increases in basal

PG levels, the alterations in H-1 receptor responsiveness, and Ca^{2+}-dependent secretion processes.

In view of the possible contributions of PGs to some of the symptoms following irradiation, further efforts are being directed toward (a) delineating the mechanisms that regulate the types and amounts synthesized and (b) further clarifying their role in the pathologic events constituting radiation injury.

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